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The need for collaboration in the future delivery of improved therapies for patients ☆

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The defining issue for the improvement of health care in the future, both in Europe and around the world, is the need for enhanced collaboration. This is vital if we want to deliver true medical innovation to patients with unmet and intractable medical conditions and do so in a predictable and cost-effective manner.

All disciplines that are involved in this worthy endeavour must find better ways to work together. Obviously, this includes the industry to which I have belonged for many years, but also regulators, prescribers, patients, payers, academics, and public and private enterprises.

Trying to create such collaborations is a challenge. If it had been easy we would have done it a long time ago. However, I do think that the advent of stratified (sometimes referred to as 'personalised') medicines provide a long awaited impetus to such drive interdisciplinary engagement.

By stratified medicines, what I am referring to are medicines that can be specifically targeted to sub-populations of patients on the basis of their genetic, metabolic and molecular profiles. The question is why stratified medicine should provide such a common focus across the healthcare sector? In order to understand this, we should start with the evolutions currently occurring in science.

Historically, scientific discovery is an agent of change – it always has been and always will be, and nowhere more so than in the classification of disease. As an example, breast cancer was traditionally diagnosed on the basis of the location of a tumour. Now, we can better classify it using genotypic features and the resulting molecular pathology. As a result, we are now aware of at least 10 different types of breast cancer, each of which may be susceptible to different therapeutic interventions.[2]

I am sure many of you remember the introduction of a drug called Herceptin in the late 1990s. One of the first successful personalised medicines on the market, it is uniquely sensitive to cells that over-express a protein called HER2.[3] This genetic condition impacts roughly15–20% of breast cancers and Herceptin is extremely effective in treating those who have that particular type of genetic mutation.[4]

Research like this will have a dramatic effect on the practice of medicine. Gone are the days where diseases are classified merely by symptoms, now it is increasingly possible to subtype common diseases on the basis of specific and measurable biological markers and then use those markers for diagnosis. In this way, we are evolving to a more sophisticated form of classification.

What are the wider implications of this evolution in classification? Firstly, as diseases fragment, their precise molecular identities will allow for rational targeted therapies designed to interfere with specific biological processes in tightly defined patient groups.

Secondly, biomarkers (which are indicators of normal biological and pathogenic processes) will be used not just

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[2]http://www.nhs.uk/news/2012/03march/Pages/chemo-hope-from-cancer-encyclopaedia.aspx.

[3]www.ncbi.nlm.nih.gov/pmc/articles/PMC3539433/.

[4]ibid.

http://dx.doi.org/10.1016/j.hlpt.2014.10.008

for diagnosis, but also for prognosis and therapeutic decision-making. This will increase the predictability of response, and also potentially reduce unnecessary risks. Clearly, if you are introducing high efficacy targeted therapies to specific patient populations you are combining increased efficacy and reduced toxicity.[5]

Thirdly, harnessing patient-derived data will become more important. This will be not only through the use of genotypic data to increase the specificity of diagnosis, but real-world data (i.e. data gathered through real-world experience) which will allow us better to monitor the outcomes of standard clinical practice.[6]

All of this is very positive for healthcare, patients, and society at large. However, the processes by which we traditionally bring new medicines to patients are no longer keeping pace with scientific progress. Our current regulatory framework is not easily adaptable to the new personalised medicine approach which requires small patient numbers, modified data requirements and differential assessments. It is expensive and quite inflexible, making it difficult to identify small effect sizes in very large, broadly defined populations. We need new adaptive trial designs which can enable faster decision-making using fewer data points, in smaller, more tightly defined patient groups. Moreover, health technology assessment (HTA) is increasingly ill-equipped to quantify value in such patient groups. This is now hugely important as HTA and national reimbursement bodies are the real gatekeepers of patient access to new improved therapies.

It is vital for us to recognise that all of these elements, not just regulation and reimbursement, but also clinical trial design, need to be addressed collectively if we are going to make any progress in support of better patients outcomes. The traditional serial approach to drug discovery and development is not working (Fig. 1). It is time consuming – fourteen plus years in many cases.[7] Estimates vary widely but costs for development are more than a billion dollars per new drug once you have accounted for failures, and it is hugely inefficient as each stage of this process awaits data from the previous stage before a decision can be made.[8] In fact, one could say that the model is no longer fit for purpose given the opportunities presented by new scientific methods.

Europe also has an added level of complexity in that individual negotiations are required at the member state level for reimbursement which often adds years to the time when patients in Europe can actually receive a new therapy (Fig. 1).

We need a fundamental redesign of this pathway. It is no longer reasonable or sustainable for us to take fourteen or fifteen years and billions of dollars to bring new drugs to market. This is particularly true if many of those new drugs are of marginal efficacy and then, only after completing all the trials and at the point of health technology assessment, it is decided they are not valuable anyway.

R&D productivity is calculated by the number of new medicines made available per billion dollars spent in development. As outlined in a now infamous Nature Article, since 1950 the costs of the development of new therapies have doubled roughly every decade.[9] This is a depressing picture, not just for the industry but for society as a whole.

So, the question is what can we do together about this? Certainly, we need to adapt; not only the development pathway, but the regulatory and reimbursement pathways as well.

Frameworks must put patient needs first and incentivise real innovation. Clinical trial regulation in Europe has long been considered bureaucratic and inconsistent; the clinical trial directive of 2004 made things worse and is only now being addressed through changes in legislation.

Whilst the European Medicine's Agency (EMA) is taking a lead in Europe to assess the advantages of adaptive regulatory pathways, the main challenges do not rest at the EMA level. Market authorisation in Europe is no longer the defining step in the process of bringing a medicine to a patient, as nationally agreed reimbursement by the individual member states has become the critical event, and increasingly, is the major bottleneck.

Across Europe, the uptake of innovative new medicines is very slow. Member states seem to delay the reimbursement decision, thus postponing the delivery of needed medicines to patients. As well, how member states define efficacy is in question, as they often fail to account for the total benefit of a targeted, personalised medicine throughout the entire healthcare value chain, favouring instead a somewhat simplistic calculation of a cost threshold.

The good news is, for the first time in my experience, all of the stakeholders engaged in this very broad debate agree on the need for fundamental change.

Patients clearly want access to new medicines as fast as possible, and many patient groups are at the vanguard of demanding changes to these pathways. Regulators such as the EMA and the UK's MHRA are advancing flexible evaluation frameworks that increase predictability, reduce inefficiency, and stimulate innovation. Obviously, industry and regulators are trying to put in place new methodologies that, while accelerated, do not compromise patient safety.

Payers should engage earlier in discussions regarding the evidence needed to access new therapies and help shape flexible development pathways. Industry wants increased R&D productivity and clearly it also wants proper incentives for innovation. Ultimately, society at large will benefit hugely if we can insure that genuine scientific breakthroughs are translated into patient benefits as quickly as possible.

The EMA's Executive Director Guido Rasi recently stated, “Regulation today is characterized by the increasing complexity of applications for new medicines”.[10] While EMA is

[5] http://www.ncbi.nlm.nih.gov/pubmed/24789362 (accessed 06.07.14).

[6] Mark Last, Abraham Kandel; Automated Detection of Outliers in Real-World Data, http://www.researchgate.net/publication/2839421_Automated_Detection_of_Outliers_in_Real-World_Data/file/d912f50ad484f043bc.pdf (accessed 06.07.14).

[7] http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/76xx/doc7615/10-02-drugr-d.pdf (accessed 15.06.14).

[8] Forbes, Matthew Herper, “The Truly Staggering Cost Of Inventing New Drugs”, February 10, 2012.

[9] “Diagnosing the decline in pharmaceutical R&D efficiency”, Jack W. Scannell, Alex Blanckley, Helen Boldon & Brian Warrington, Nature Reviews Drug Discovery 11, 191-200 (March 2012), http://www.nature.com/nrd/journal/v11/n3/full/nrd3681.html (accessed 02.07.14).

[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/03/news_detail_001749.jsp&mid=WC0b01ac058004d5c1.